(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

BE

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 January 2002 (31.01.2002)

PCT

(10) International Publication Number
WO 02/08232 A1

(51) International Patent Classification[7]: C07D 521/00, 213/82, 401/04, 213/75, 413/04, A61K 31/4427, 31/465, A61P 25/00, 29/00

(21) International Application Number: PCT/EP01/08432

(22) International Filing Date: 20 July 2001 (20.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00115846.8 24 July 2000 (24.07.2000) EP

(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; 124 Grenzacherstrasse, CH-4070 Basle (CH).

(72) Inventors: HOFFMANN, Torsten; Kleinhueninger Strasse 15, 79576 Weil am Rhein (DE). SCHNIDER, Patrick; Stallenrain 7, CH-4104 Oberwil (CH). STADLER, Heinz; Waldhofstrasse 37, CH-4310 Rheinfelden (CH).

(74) Agent: POPPE, Regina; Grenzacherstrasse 124, CH-4070 Basle (CH).

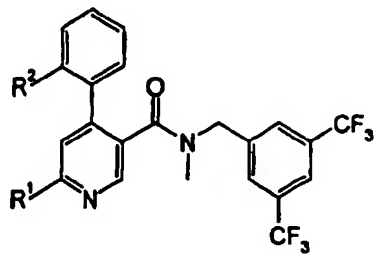
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

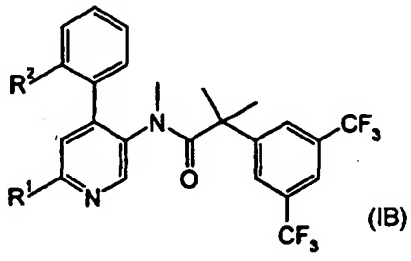
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

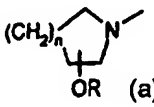
(54) Title: 4-PHENYL-PYRIDINE DERIVATIVES AS NEUROKININ-1 RECEPTOR ANTAGONISTS



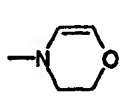
(IA)



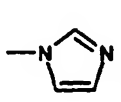
(IB)



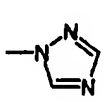
(a)



(b)



(c)



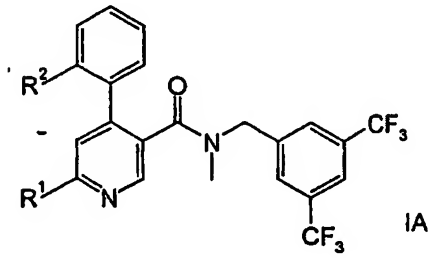
(d)

(57) Abstract: The invention relates to compounds of general formulas (IA) or (IB) wherein R^1 is (a), (b), (c), (d) or is $-NH(CH_2)_2OH$, $-NR^3C(O)CH_3$ or $-NR^3C(O)$-cyclopropyl; R^2 is methyl or chloro; R^3 is hydrogen or methyl; R is hydrogen or $-(CH_2)_2OH$; and n is 1 or 2 and pharmaceutically acceptable acid addition salts thereof. These compounds have a good affinity of the NK-1 receptor and therefore they may be used in the treatment or prevention of diseases, related to this receptor.

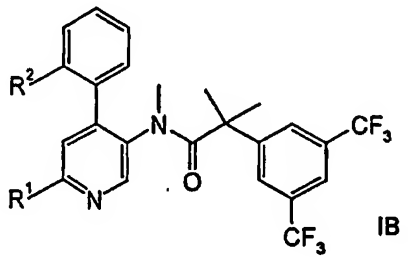
WO 02/08232 A1

4-PHENYL-PYRIDINE DERIVATIVES AS NEUROKININ-1 RECEPTOR ANTAGONISTS

The present invention relates to compounds of the general formulas

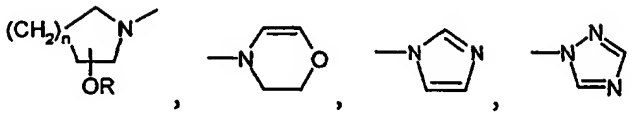

IA

or


IB

wherein

R^1 is


or is

$-NH(CH_2)_2OH$, $-NR^3C(O)CH_3$ or $-NR^3C(O)$-cyclopropyl;

R^2 is methyl or chloro;

R^3 is hydrogen or methyl;

R is hydrogen or $-(CH_2)_2OH$; and

n is 1 or 2

and to pharmaceutically acceptable acid addition salts thereof.

Compounds, similar to those described in the present application, have been described in EP 1035115.

The compounds of formulas IA and IB and their salts are characterized by valuable therapeutic properties. It has been surprisingly found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor. Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the

latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The receptor for substance P is a member of the superfamily of G protein-coupled receptors.

The neuropeptide receptor for substance P (NK-1) is widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes.
The central and peripheral actions of the mammalian tachykinin substance P have been associated with numerous inflammatory conditions including migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease as well as mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders such as Parkinson's disease (Neurosci. Res., 1996, 7, 187-214), anxiety (Can. J. Phys., 1997, 75, 612-621) and depression (Science, 1998, 281, 1640-1645).
Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases reviewed in "Tachykinin Receptor and Tachykinin Receptor Antagonists", J. Auton. Pharmacol., 13, 23-93, 1993.

Furthermore, Neurokinin 1 receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinin, in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (WO 95/16679, WO 95/18124 and WO 95/23798).

The neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment of induced vomiting.

In addition, in The New England Journal of Medicine, Vol. 340, No. 3 190-195, 1999 has been described the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.

Furthermore, US 5,972,938 describes a method for treating a psychoimmunologic or a psychosomatic disorder by administration of a tachykinin receptor, such as NK-1 receptor antagonist.

The usefulness of neurokinin 1 receptor antagonists for the treatment of certain forms of urinary incontinence is further described in "Neuropeptides, 32(1), 1-49, (1998)" and "Eur. J. Pharmacol., 383(3), 297-303, (1999)".

The compounds of formulas IA and IB can also be used in form of their prodrugs. Examples are esters, N-oxides, phosphate esters, glycoamide esters, glyceride conjugates and the like. The prodrugs may add to the value of the present compounds advantages in adsorption, pharmacokinetics in distribution and transport to the brain.

Objects of the present invention are the compounds of formulas IA and IB and pharmaceutically acceptable salts thereof, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier or in the manufacture of corresponding medicaments.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders or emesis by the administration of NK-1 receptor antagonists. A major depressive episode has been defined as being a period of at least two weeks during which, for most of the day and nearly every day, there is either depressed mood or the loss of interest or pleasure in all, or nearly all activities.

Exemplary preferred are compounds of formula IA, in which R^2 is methyl, for example the following compounds:

N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-6-[1,2,4]triazol-1-yl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-(2-hydroxy-ethylamino)-N-methyl-4-o-tolyl-nicotinamide,
4-hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-hydroxy-ethoxy)-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide or

(R)-N-(3,5-bis-trifluoromethyl-benzyl)-6-(3-hydroxy-pyrrolidin-1-yl)-N-methyl-4-o-tolyl-nicotinamide.

Further preferred are compounds of formula IA, in which R^2 is chloro.

An example of such compound is:

4'-(2-chloro-phenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

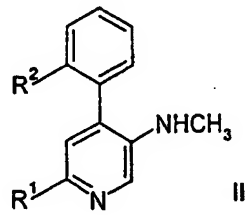
Exemplary preferred are compounds of formula IB, in which R^2 is methyl, for example the following compounds:

2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-ethylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2,3-dihydro-[1,4]oxazin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
N-(6-acetylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide,
N-[6-(acetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide,
cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-amide,
cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-methyl-amide or
2-(3,5-bis-trifluoromethyl-phenyl)-N-(6-imidazol-1-yl-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide.

Further preferred are compounds of formula IB, in which R^2 is chloro, for example the following compound:
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(2-hydroxy-ethylamino)-pyridin-3-yl]-N-methyl-isobutyramide.

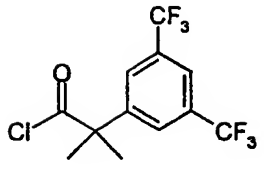
The present compounds of formulas IA and IB and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



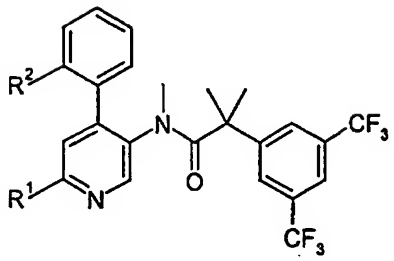
II

with a compound of formula



III

to a compound of formula

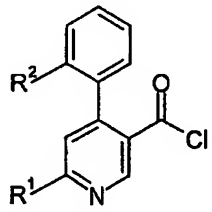


IB

wherein R' and R^2 have the significances given above,

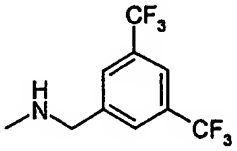
or

b) reacting a compound of formula



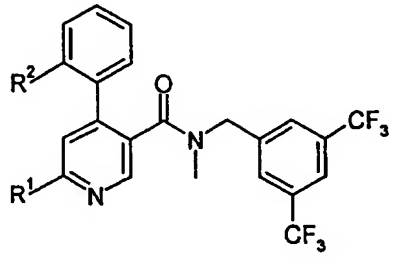
IV

with a compound of formula



V

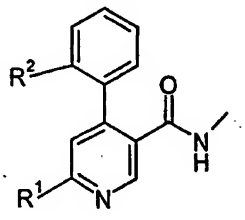
to give a compound of formula



IA

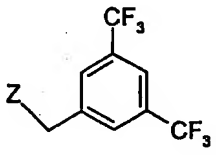
wherein R^1 and R^2 have the significances given above, or

c) reacting a compound of formula



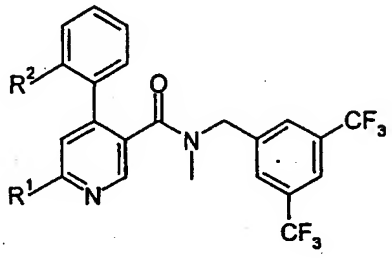
VI

with a compound of formula



VII

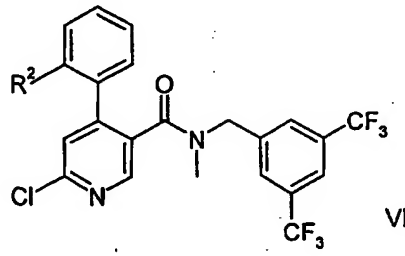
to a compound of formula



IA

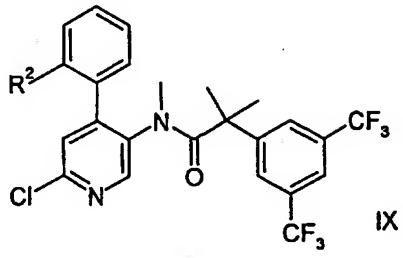
wherein Z is Cl, Br, I, $-OS(O)_2C_6H_4CH_3$ or $-OS(O)_2CH_3$ and the other definitions of substituents are given above, or

d) reacting a compound of formula



VIII

or

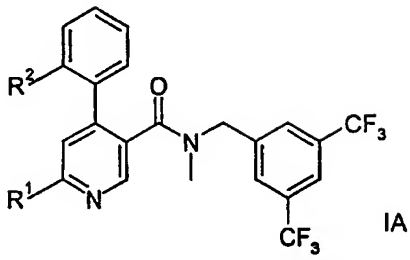


IX

with a compound of formula

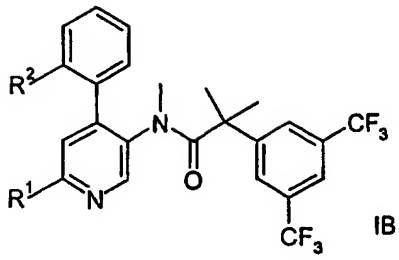
R^1H XIV

to a compound of formulas



IA

or



IB

wherein the definition of substituents is given above,

and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

In accordance with process variant a) DIPEA (N-ethyldiisopropyl-amine) is added to a mixture of a compound of formula II and a compound of formula III in dichloromethane and the mixture is stirred at temperatures between 35-40 °C. The desired compound of formula IB is isolated after purification in good yields.

Process variant b) describes the reaction of a compound of formula IV with a compound of formula V to a compound of formula IA. The reaction is carried out in conventional manner, for example in a solvent, such as a mixture of toluene and triethyl-amine. The mixture is refluxed for about 1 hour.

Process variant c) describes the reaction of a compound of formula VI with a compound of formula VII to a compound of formula IA. This reaction is carried out by deprotonation of a compound of formula VI with KHMDS (potassium hexamethyldisilazide) and subsequent addition of a compound of formula VII. A suitable solvent is tetrahydrofuran. The reaction is carried out at room temperature.

A further method for the preparation of a compound of formula IA or IB is described in process variant d). A compound of formulas VIII or IX is treated with a compound of formula XIV, which is, for example, 1,2,4-triazole, ethanolamine, 4-hydroxypiperidine, (R)-3-pyrrolidinol or morpholine. The reaction is carried out in THF, usually at 80 – 140 °C.

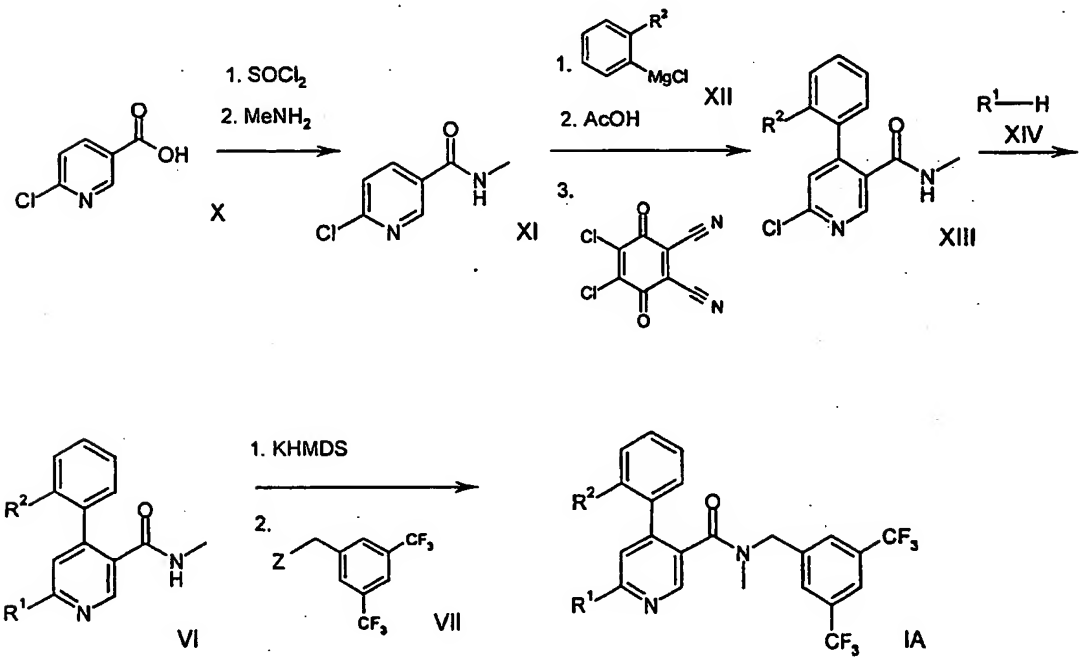
The salt formation is effected at room temperature in accordance with methods which are known per se and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids come into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrates, acetates, maleates, succinates, methan-sulphonates, p-toluenesulphonates and the like are examples of such salts.

The following schemes 1-3 describe the processes for preparation of compounds of formulas IA and IB in more detail. The starting materials are known compounds or may be prepared according to methods known in the art.

In the schemes the following abbreviations have been used:

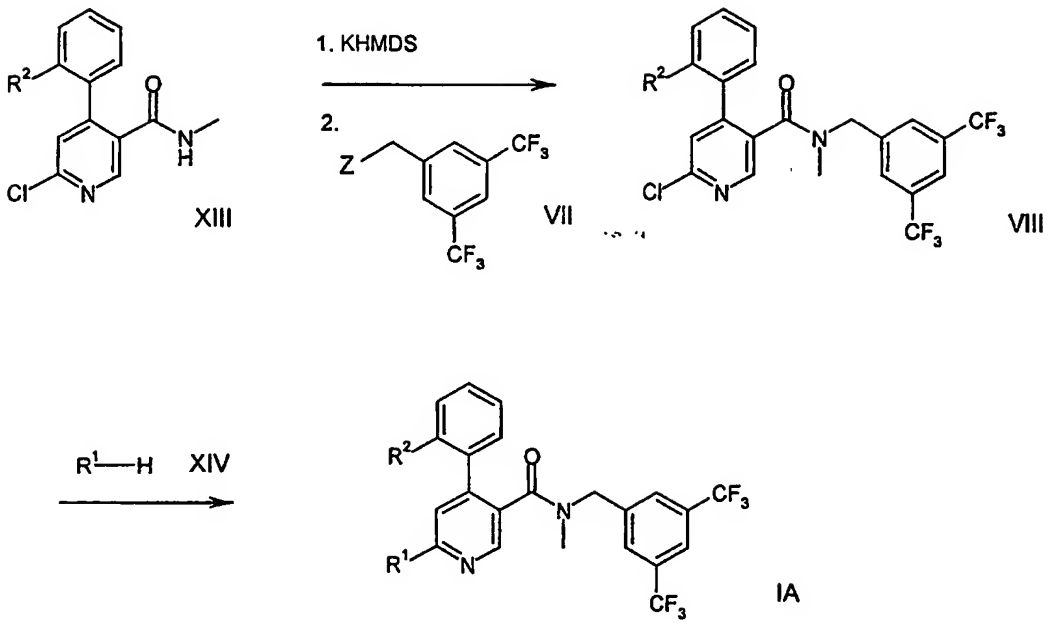
PivCl	pivaloyl chloride
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylene diamine
DIPEA	N-ethyldiisopropyl-amine
KHMDS	potassium hexamethyldisilazide

Scheme 1



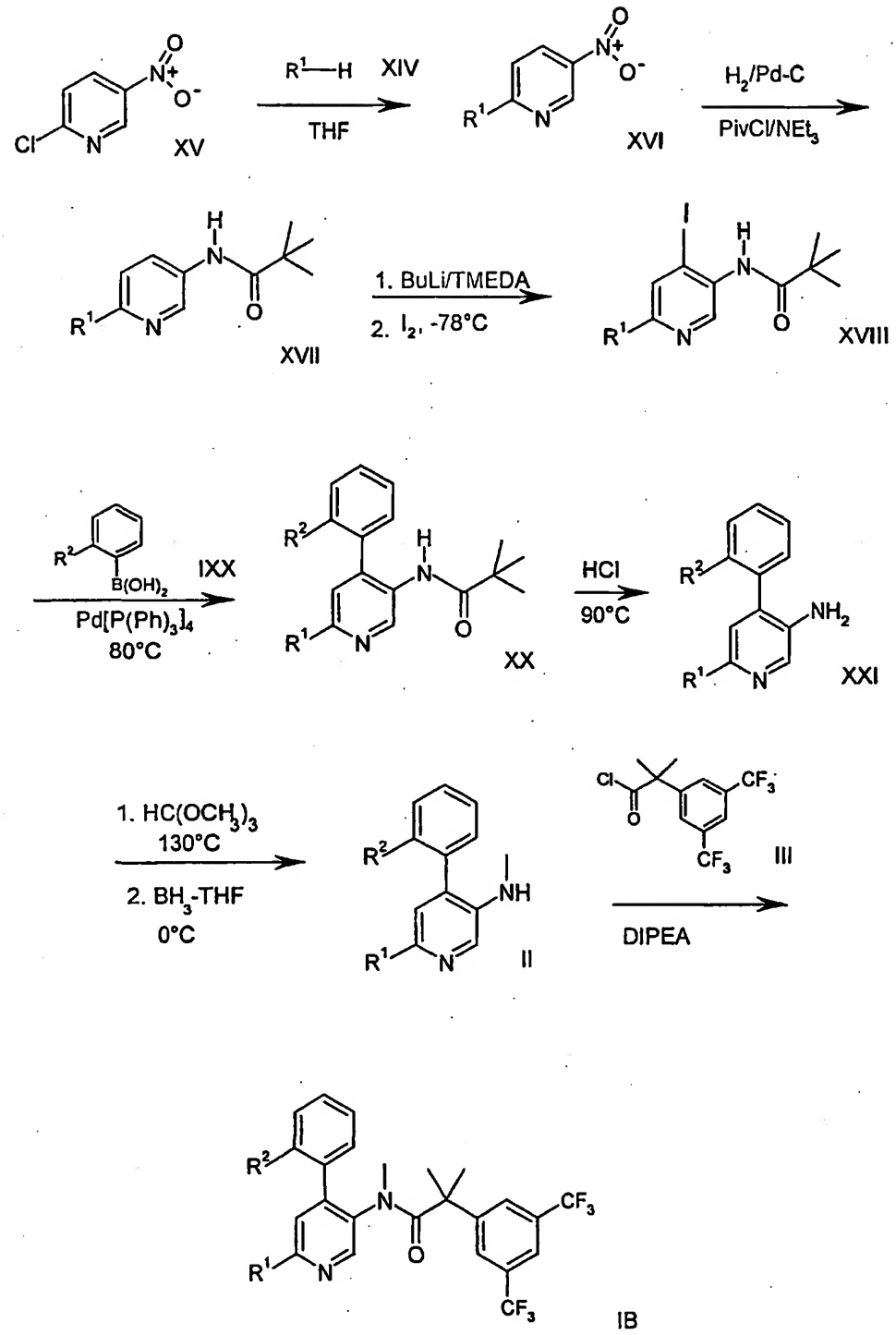
The definition of substituents is described above.

Scheme 2



The definition of substituents is described above.

Scheme 3



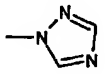
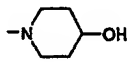
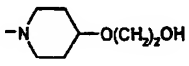
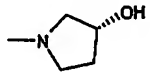
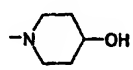
The definition of substituents is described above.

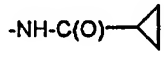
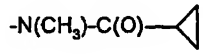
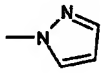
As mentioned earlier, the compounds of formulas IA and IB and their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor.

The compounds were investigated in accordance with the tests given hereinafter.

The affinity of test compounds for the NK_1 receptor was evaluated at human NK_1 receptors in CHO cells infected with the human NK_1 receptor (using the Semliki virus expression system) and radiolabelled with [^{3}H]substance P (final concentration 0.6 nM). Binding assays were performed in HEPES buffer (50 mM, pH 7.4) containing BSA (0.04 %) leupeptin (8 µg / ml), $MnCl_2$ (3 mM) and phosphoramidon (2 µM). Binding assays consisted of 250 µl of membrane suspension (1.25 x10^5 cells / assay tube), 0.125 µl of buffer of displacing agent and 125 µl of [^{3}H]substance P. Displacement curves were determined with at least seven concentrations of the compound. The assay tubes were incubated for 60 min at room temperature after which time the tube contents were rapidly filtered under vacuum through GF/C filters presoaked for 60 min with PEI (0.3 %) with 2 x 2 ml washes of HEPES buffer (50 mM, pH 7.4). The radioactivity retained on the filters was measured by scintillation counting. All assays were performed in triplicate in at least 2 separate experiments.

The affinity to the NK-1 receptor, given as pKi, is in the scope of 8.40 - 9.24 for the described compounds.

pKi	R^1	R^2	Formula	Expl.
8.4		CH_3	IA	1
8.87	$-NH(CH_2)_2OH$	CH_3	IA	2
8.91		CH_3	IA	3
9.03		CH_3	IA	4
9.24		CH_3	IA	5
9.18		Cl	IA	6

9.16	$-NH(CH_2)_2OH$	CH_3	IB	7
9.14	$-NH(CH_2)_2OH$	Cl	IB	8
8.83		CH_3	IB	9
8.6	$-NHC(O)CH_3$	CH_3	IB	10
8.71	$-N(CH_3)C(O)CH_3$	CH_3	IB	11
8.65		CH_3	IB	12
8.87		CH_3	IB	13
8.65		CH_3	IB	14

The compounds of formulas IA and IB as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formulas IA and IB and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01 – 20 mg/kg/day, with a dosage of 0.1 – 10 mg/kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7 – 1400 mg per day, preferrably between 7 and 700 mg per day.

The following Examples illustrate the present invention without limiting it. All temperatures are given in degrees Celsius.

Example 1

N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-6-[1,2,4]triazol-1-yl-nicotinamide

a) 6-Chloro-N-methyl-nicotinamide

To 50 g (317 mmol) of 2-chloronicotinic acid was added 230 ml (3.16 mol) thionyl chloride at 0 °C. After heating the mixture at reflux for 2 h excess thionyl chloride was removed by distillation. The oily brown residue was dissolved in 250 ml dichloromethane. The solution was treated with methylamine gas at 0 °C until no exothermic reaction was observed any longer. The resulting suspension was diluted with 1000 ml dichloromethane/water. The layers were separated and the aqueous layer extracted with three 300 ml portions of dichloromethane. Drying of the organic layer with sodium sulfate and concentration gave 53.2 g (98 %) of the title compound as a light yellow solid.

MS m/e (%): 171 ($M+H^+$, 15).

b) 6-Chloro-N-methyl-4-o-tolyl-nicotinamide

To a solution of 3.41 g (20.0 mmol) 6-chloro-N-methyl-nicotinamide in 80 ml tetrahydrofuran 50 ml (50 mmol) of a 1 M solution of o-tolyl magnesium chloride in tetrahydrofuran was added dropwise at 0 °C. After completed addition the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The mixture was again cooled to 0 °C, followed by the dropwise addition of 5.7 ml (100 mmol) acetic acid and a solution of 5.1 g (22 mmol) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 18 ml tetrahydrofuran. After completed addition the reaction mixture was allowed to warm to room temperature and stirred for 15 min. Addition of 30 ml 2 N aqueous sodium hydroxide solution was followed by dilution with 1 l ethyl acetate and 200 ml water. The layers were separated and the organic layer washed with 4 250-ml portions of 2 N aqueous sodium hydroxide solution. The combined aqueous layers were extracted with 3 500-ml portions of ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium chloride solution and dried with sodium sulfate. Concentration gave 5.44 g of a brown-red oil. Flash column chromatography afforded 2.15 g (41.3 %) of the title compound as a light yellow solid.

MS m/e (%): 260 ($M^{\cdot+}$, 11). M.p. 91 – 93 °C.

c) N-(3,5-Bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide

To a solution of 10.0 g (38.4 mmol) 6-chloro-N-methyl-4-o-tolyl-nicotinamide in 190 ml tetrahydrofuran 46 ml of a 1 M solution (46 mmol) of potassium hexamethyldisilazide in tetrahydrofuran were added at 0 °C. After 30 min, 8.5 ml (46 mmol) 3,5-bis(trifluoromethyl)benzyl bromide were added dropwise to the resulting suspension. After completed addition the ice-water cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 2h the reaction was quenched with water. The mixture was adjusted to pH 3 with 1 M aqueous hydrochloric acid solution and stirred for 10 min. Basification with 1 M aqueous sodium hydroxide solution to pH 8 was followed by concentration to remove tetrahydrofuran. The aqueous residue was extracted with four portions of dichloromethane. The combined organic extracts were dried with sodium sulfate and concentrated to give 21.4 g of crude product. Column chromatography afforded 18.4 g (98.5 %) of the title compound as a white solid.

MS m/e (%): 485 ($[M-H]^+$, 2).

d) N-(3,5-Bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-6-[1,2,4]triazol-1-yl-nicotinamide

A mixture of 1.00 g (2.05 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide and 1.42 g (20.5 mmol) 1,2,4-triazole was stirred at 130 °C for 36 h. After cooling to room temperature the crude mixture was purified by flash chromatography to give 0.93 g (87 %) of the title compound as a white solid.

MS m/e (%): 520 ($M+H^+$, 100).

Example 2

N-(3,5-Bis-trifluoromethyl-benzyl)-6-(2-hydroxy-ethylamino)-N-methyl-4-o-tolyl-nicotinamide

A mixture of 0.837 g (1.72 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide and 5.0 ml (83 mmol) ethanolamine was stirred at 100 °C for 48 h. After cooling to room temperature excess ethanolamine was removed under reduced pressure. The residue was dissolved in a mixture of ethyl acetate and saturated aqueous sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution and water, dried with sodium sulfate and concentrated to give 0.8 g of crude product. Flash chromatography afforded 0.650 g (73.9 %) of the title compound as a white solid.

MS m/e (%): 512 ($M+H^+$, 100).

Example 3

4-Hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

A mixture of 10.0 g (20.5 mmol) N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide, 3.1 g (31 mmol) 4-hydroxypiperidine, 10.6 ml (62 mmol) N-ethyldiisopropylamine and 0.13 g (1.0 mmol) 4-(N,N-dimethylamino)-pyridine was stirred at 140 °C for 70 h. After cooling to room temperature the residue was dissolved in a mixture of dichloromethane and water. The layers were separated and the aqueous layer was extracted with four portions of dichloromethane. The combined organic extracts were dried with sodium sulfate and concentrated to give 11.1 g of crude product. Flash chromatography afforded 9.0 g (80 %) of the title compound as a white solid.

MS m/e (%): 552 ($M+H^+$, 100), M.p. 150 – 152 °C.

Example 4

4-(2-Hydroxy-ethoxy)-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

a) 4-[2-(tert-Butyl-dimethyl-silanyloxy)-ethoxy]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a suspension of 48 mg (1.1 mmol) sodium hydride (55 % in oil) and 17 mg (0.045 mmol) tetrabutylammonium iodide in 4.5 ml dry tetrahydrofuran a solution of 0.50 g (0.91 mmol) 4-(2-hydroxy-ethoxy)-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 4.5 ml dry tetrahydrofuran was added dropwise at 0 °C under argon. After completed addition the reaction mixture was allowed to warm to room temperature. After 1h 0.23 ml (1.1 mmol) (2-bromoethoxy)-tert-butyl-dimethylsilane were added dropwise. The reaction mixture was heated to 50 °C and stirred over night. After cooling to room temperature the reaction was quenched by addition of 5 ml water. The pH was adjusted to 2 by addition of 1 M aqueous hydrochloric acid solution. After 5 min. the mixture was basified with a saturated aqueous sodium carbonate solution and extracted with 3 portions of ethyl acetate. The combined organic extracts were washed with water, dried with sodium sulfate and concentrated to give 0.79 g of a yellow oil. Flash chromatography afforded 0.13 g (20 %) of the title compound as a white solid.

MS m/e (%): 710 ($M+H^+$, 100).

Starting material (0.21 g, 42 %) was recovered.

b) 4-(2-Hydroxy-ethoxy)-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of 115 mg (0.162 mmol) (4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide in 3 ml dry tetrahydrofuran were added 0.17 ml (0.17 mmol) of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran at room temperature under argon. After stirring over night the reaction mixture was diluted with ethyl acetate and washed with water. The layers were separated and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic extracts were washed with two portions of water, dried with magnesium sulfate and concentrated to give 111 mg of a yellow oil. Flash chromatography afforded 59 mg (61 %) of the title compound as a white solid.

MS m/e (%): 596 ($M+H^+$, 100).

Example 5

(R)-N-(3,5-Bis-trifluoromethyl-benzyl)-6-(3-hydroxy-pyrrolidin-1-yl)-N-methyl-4-o-tolyl-nicotinamide

The title compound was obtained as a colorless amorphous mass in comparable yield according to the procedure described above for the preparation of 4-hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide using (R)-3-pyrrolidinol instead of 4-hydroxypiperidine.

MS m/e (%): 538 ($M+H^+$, 100).

Example 6

4'-(2-Chloro-phenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

a) 4-Hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide

A mixture of 8.51 g (49.9 mmol) 6-chloro-N-methyl-nicotinamide, 5.66 g (54.9 mmol) 4-hydroxypiperidine, 26.1 ml (150 mmol) N-ethyldiisopropylamine and 0.31 g (2.5 mmol) 4-(N,N-dimethylamino)-pyridine was heated at reflux over night. After cooling to room temperature the crude mixture was transferred to a flash chromatography column. Elution afforded 10.1 g (86.1 %) of the title compound as a light yellow solid.

MS m/e (%): 236 ($M+H^+$, 100).

b) 4-(tert-Butyl-dimethyl-silanyloxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide

A mixture of 10.1 g (42.9 mmol) 4-hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide, 8.0 g (52 mmol) tert-butyldimethylchlorosilane and 6.5 g (94 mmol) imidazole in 90 ml N,N-dimethylformamide was stirred at room temperature over night. The reaction was quenched with water. The resulting suspension was extracted with ethyl acetate. The organic extract was washed with 3 portions of water. The combined aqueous layers were extracted with 3 portions of dichloromethane. The combined organic extracts were dried with sodium sulfate, concentrated and dried in vacuo (0.5 mbar) at 80 °C. Flash column chromatography afforded 14.6 g (97.3 %) of the title compound as a light yellow solid.

MS m/e (%): 349 (M^+, 21).

c) 4-(tert-Butyl-dimethyl-silanyloxy)-4'-iodo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide

To a solution of 500 mg (1.43 mmol) 4-(tert-butyl-dimethyl-silanyloxy)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide, 1.7 ml (11 mmol) N,N,N',N'-tetramethyl-ethylenediamine and 1.0 ml (5.7 mmol) 2,2,6,6-tetramethylpiperidine in 9.5 ml dry tetrahydrofuran 7.2 ml (11 mmol) of a 1.6 M solution of n-butyllithium in hexanes were added dropwise during 10 min. at –78 °C under argon. The resulting solution was stirred at –78°C for 30 min., warmed to –20 °C and stirred at this temperature for 3 h. After cooling the reaction mixture to –78 °C a solution of 2.92 g (11.5 mmol) iodine in 7 ml dry tetrahydrofuran was added dropwise under argon. The resulting suspension was kept at –78 °C for 2 h and subsequently allowed to warm to room temperature over 1h. The suspension was poured into a solution of 12.4 g (50.0 mmol) sodium thiosulfate pentahydrate in 50 ml ice-water. The resulting yellow suspension was extracted with two 250-ml portions of tert-butyl methyl ether. The combined organic extracts were washed with 2 portions of a saturated aqueous ammonium chloride solution, dried with sodium sulfate and concentrated. Flash chromatography afforded 495 mg (72.8 %) of the title compound as an off-white amorphous mass.

MS m/e (%): 476 ($M+H^+$, 100).

d) 4-(tert-Butyl-dimethyl-silanyloxy)-4'-(2-chloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide

A mixture of 480 mg (1.01 mmol) 4-(tert-butyl-dimethyl-silanyloxy)-4'-iodo-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide, 174 mg (1.11 mmol) 2-chlorophenylboronic acid, 6 ml dimethoxyethane and 1 ml of a 2 M aqueous solution of sodium carbonate was deoxygenated by three freeze-thaw cycles. After addition of 60 mg (0.052 mmol) tetrakis(triphenylphosphine)palladium(0) the reaction mixture was stirred at 90 °C for 3 h. Cooling to room temperature was followed by dilution with water and extraction with ethyl acetate. The organic extract was washed with saturated aqueous sodium carbonate and sodium chloride solutions, dried with sodium sulfate and concentrated. Column chromatography afforded 425 mg (91.5 %) of the title compound as an off-white solid.

MS m/e (%):460 ($M+H^+$, 100).

e) 4-(tert-Butyl-dimethyl-silanyloxy)-4'-(2-chloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

The title compound was obtained as off-white foam in 49 % yield according to the procedure described above for the preparation of N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide using 4-(tert-butyl-dimethyl-silanyloxy)-4'-(2-chloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid methylamide instead of 6-chloro-N-methyl-4-o-tolyl-nicotinamide.
MS m/e (%): 685 (M^{+}, 40).

f) 4'-(2-Chloro-phenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

The title compound was obtained as a white solid in 82 % yield according to the procedure described above for the preparation of 4-(2-hydroxy-ethoxy)-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide using 4-(tert-butyl-dimethyl-silanyloxy)-4'-(2-chloro-phenyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide instead of (4-[2-(tert-butyl-dimethyl-silanyloxy)-ethoxy]-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.
MS m/e (%): 572 ($M+H^{+}$, 100).

Example 7

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-ethylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

a) 4-(5-Nitro-2-pyridyl)-morpholine

To a solution of 20 g (126 mmol) of 2-chloro-5-nitropyridine in 150 ml tetrahydrofuran were added dropwise 27 ml (315 mmol) morpholine within 10 min. The reaction mixture was refluxed for additional 2 h. After cooling to room temperature, the solvent was removed in vacuo and the residue was re-dissolved in 200 ml ethyl acetate. The organic phase was washed with 200 ml 1 N sodium bicarbonate solution, dried (magnesium sulfate) and evaporated to give 27.3 g (quantitative) of the title compound as a yellow solid.
M.p. 142-143 °C.

b) 2,2-Dimethyl-N-(6-morpholin-4-yl-pyridin-3-yl)-propionamide

To a solution of 27.3 g (126 mmol) of 4-(5-nitro-2-pyridyl)-morpholine in 600 ml methanol were added 2.5 g of 10 % of palladium on activated charcoal. The reaction mixture was hydrogenated (room temperature to ca. 45 °C, 1 bar) until the theoretical amount of hydrogen was taken up (about 3 h). The catalyst was filtered off and was washed twice with 100 ml portions of methanol. The filtrate was evaporated in vacuo to give 22.6 g

of a purple oil which consisted to ca. 95 % of the desired aniline derivative according to analysis by thin layer chromatography.

This crude product was dissolved in a mixture of 240 ml tetrahydrofuran and 60 ml diethyl ether. After cooling to 0 °C, 26 ml (189 mmol) of triethylamine were added in one portion. Stirring was continued while 23 g (189 mmol) of pivaloyl chloride were added dropwise within a period of 10 min. The ice bath was removed and the reaction mixture was stirred for 1 h at room temperature. Then, the solvent was removed in vacuo and the residue was suspended in 200 ml 1 N sodium bicarbonate solution. The product was extracted three times with 200 ml portions of dichloromethane, dried (sodium sulfate) and evaporated. Recrystallization of the solid residue from ethyl acetate/hexane 1:8 gave 28.6 g (86 %) of the title compound as white crystals.

MS m/e (%): 264 ($M+H^+$, 100).

c) N-(4-Iodo-6-morpholin-4-yl-pyridin-3-yl)-2,2-dimethyl-propionamide

A solution of 28.4 g (108 mmol) 2,2-dimethyl-N-(6-morpholin-4-yl-pyridin-3-yl)-propionamide and 49 ml (324 mmol) N,N,N',N'-tetramethylethylenediamine under argon in 600 ml tetrahydrofuran was cooled in a dry ice bath to –78 °C. Within 1 h, 202 ml (324 mmol) of a 1.6 N n-butyllithium solution in hexane were added dropwise. The reaction mixture was allowed to warm up to –35 °C overnight. After cooling again to –78 °C, 37 g (146 mmol) iodine dissolved in 60 ml tetrahydrofuran were added dropwise during 15 min. The dry ice bath was replaced by an ice bath and a solution of 90 g (363 mmol) sodium thiosulfate pentahydrate in 250 ml water were added within 10 min when the temperature of the reaction mixture had reached 0 °C. Then, 1000 ml diethyl ether were added and the organic layer was separated. The aqueous layer was extracted twice with 500 ml dichloromethane and the combined organic layers were dried (magnesium sulfate) and evaporated. Flash chromatography gave 15.6 g (37 %) of the title compound as a light brown oil which crystallized upon standing at room temperature.

MS m/e (%): 389 (M^+, 71), 358 (25), 304 (43), 57 (100).

d) 2,2-Dimethyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-propionamide

A mixture of 3.50 g (9.0 mmol) N-(4-iodo-6-morpholin-4-yl-pyridin-3-yl)-2,2-dimethyl-propionamide, 35 ml toluene, 18 ml 2 N sodium carbonate solution, 312 mg (0.27 mmol) tetrakis(triphenylphosphine)palladium(0) and 1.34 g (9.9 mmol) o-tolylboronic acid was heated under argon at 80 °C for 12 h. After cooling to room temperature, the aqueous phase was separated and washed twice with ethyl acetate. The combined organic layers

were washed with 50 ml brine, dried (sodium sulfate) and evaporated. Purification by flash-chromatography gave 3.23 g (quantitative) of the title compound as a white foam.

MS m/e (%): 354 ($M+H^+$, 100).

e) 6-Morpholin-4-yl-4-o-tolyl-pyridin-3-ylamine

A suspension of 2.93 g (8.28 mmol) 2,2-dimethyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-propionamide in 80 ml 3 N hydrochloric acid solution and 5 ml 1-propanol was heated to 90-95 °C overnight. The reaction mixture was cooled to room temperature, washed with three 20 ml portions diethyl ether and filtered over celite. The filtrate was diluted with 20 ml water and was adjusted to pH 7-8 by addition of 28 % sodium hydroxide solution under ice cooling. The product was extracted with four 100 ml portions of dichloromethane. The combined organic layers were washed with 50 ml brine, dried (magnesium sulfate) and evaporated to give 2.31 g (quantitative) of the title compound as a white foam.

MS m/e (%): 269 (M^+, 100).

f) Methyl-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine

A solution of 2.24 g (8.3 mmol) 6-morpholin-4-yl-4-o-tolyl-pyridin-3-ylamine in 17 ml trimethyl orthoformate and 3 drops trifluoroacetic acid was heated for 2 h at 130 °C. The reaction mixture was evaporated and dried in vacuo for 30 min. The residual oil was dissolved in 5 ml tetrahydrofuran and was added dropwise under ice cooling to 630 mg (16.6 mmol) lithium aluminum hydride in 20 ml tetrahydrofuran. The reaction mixture was stirred for 1 h at room temperature, cooled to 0 °C again and acidified (pH 1-2) by addition of 28 % hydrochloric acid solution. After stirring for 5 min, 28 % sodium hydroxide solution was added to reach pH 10. The solution was filtered over celite, evaporated and purified by flash chromatography to give 1.56 g (66 %) of the title compound as a white foam.

MS m/e (%): 283 (M^+, 100).

g) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide

A solution of 1.46 g (5.15 mmol) methyl-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine and 1.32 ml (7.73 mmol) N-ethyldiisopropylamine in 15 ml dichloromethane was cooled in an ice bath and 1.8 g (5.67 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl chloride were added dropwise. The reaction mixture was warmed to 35-40 °C

for 3 h, cooled to room temperature again and was stirred with 25 ml saturated sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography to give 2.9 g (quantitative) of the title compound as white crystals. M.p. 131-132 °C.

h) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-ethylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

A mixture of 1.0 g (1.76 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide, 100 mg (0.48 mmol) ruthenium(III)chloride hydrate, 832 mg (3.87 mmol) sodium periodate, 3.5 ml carbon tetrachloride, 3.5 ml acetonitrile and 5.3 ml water was stirred for 4 days at room temperature. Dichloromethane was added, the organic layer was separated, washed with sodium hydrogensulfite solution and filtered over celite. To the filtrate were added 10 ml 1 N potassium hydroxide solution and 20 ml methanol. After heating the mixture for 1 h at 40 °C, the solvents were removed in vacuo and the residue was purified by flash-chromatography to give 352 mg (37 %) of the title compound as light brown foam.

MS m/e (%): 540 ($M+H^+$, 100).

Example 8

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(2-hydroxy-ethylamino)-pyridin-3-yl]-N-methyl-isobutyramide

The title compound was obtained as light brown foam in comparable yield according to the procedures described above for the preparation of 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-ethylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide using 2-chloroboronic acid instead of o-tolylboronic acid in step d).

MS m/e (%): 560 ($M+H^+$, 100).

Example 9

2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2,3-dihydro-[1,4]oxazin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

a) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(3-oxo-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide

To an ice-cooled suspension of 1.2 g (7.1 mmol) ruthenium(IV)oxide hydrate in a mixture of 50 ml carbon tetrachloride and 50 ml water were added 9.0 g (42 mmol) sodium

periodate. After stirring for 30 min the organic layer was separated and the aqueous layer was extracted twice with 10-ml portions of carbon tetrachloride. The combined organic layers were filtered over celite, cooled to 0 °C and were added slowly to an ice-cooled solution of 2.0 g (3.54 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide in 20 ml carbon tetrachloride. The mixture was stirred for additional 15 min at 0 °C, was filtered over celite and was evaporated. The residue was purified by flash-chromatography and gave 704 mg (34 %) of the title compound as colourless foam.

MS m/e (%): 580 ($M+H^+$, 100).

b) (RS)-2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

To an ice-cooled solution of 494 mg (0.852 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(3-oxo-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide in 5 ml methanol and 5 ml tetrahydrofuran were added 635 mg (1.70 mmol) cerium(III)chloride heptahydrate. After stirring for 5 min, 64 mg (1.70 mmol) sodium borohydride were added in two portions within 2 min. After stirring for 3 h at 0 °C, 1 ml acetone was added and stirring was continued for 10 min. The solvent was removed, the residue was re-dissolved in ethyl acetate and the organic phase was washed with saturated sodium carbonate solution, dried (magnesium sulfate) and evaporated. The crude material was purified by flash-chromatography to give 87 mg (16 %) of the title compound as white crystals.
MS m/e (%): 582 ($M+H^+$, 100).

c) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-[6-(2,3-dihydro-[1,4]oxazin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide

To a solution of 65 mg (0.11 mmol) (RS)-2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide in 2 ml chloroform were added a few drops of a 2.3 N hydrochloric acid solution in diethyl ether. After stirring at room temperature for 2 h, the organic layer was washed with saturated sodium carbonate solution, dried (magnesium sulfate) and evaporated. The residue was purified by flash-chromatography to give 47 mg (75 %) of the title compound as white foam.

MS m/e (%): 564 ($M+H^+$, 100).

Example 10

N-(6-Acetylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

a) N2-Benzyl-N5-methyl-4-o-tolyl-pyridine-2,5-diamine

The title compound was prepared following the procedures described above for the synthesis of methyl-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine.

MS m/e (%): 304 ($M+H^+$, 100).

b) Benzyl-(5-methylamino-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester

To a solution of 2.03 g (6.7 mmol) N2-benzyl-N5-methyl-4-o-tolyl-pyridine-2,5-diamine in 100 ml dichloromethane and 40 ml N-ethyldiisopropylamine a solution of 2.1 ml (14.09 mmol) benzyl chloroformate in 50 ml dichloromethane was added dropwise at 0 °C. After stirring for 2 h at room temperature the reaction mixture was washed with water (2 x 50 ml), brine (50 ml), dried (magnesium sulfate) and evaporated. Chromatography of the residue afforded 2.36 g (80 %) of the title compound as light brown crystals. M.p. 110-112 °C.

MS m/e (%): 438 ($M+H^+$, 100).

c) Benzyl-(5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester

To a solution of 1.075 g (2.5 mmol) benzyl-(5-methylamino-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester in 10 ml dichloromethane and 1 ml N-ethyldiisopropylamine was added dropwise at 0 °C a solution of 1.15 g (3.5 mmol) 2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionic acid chloride in 2 ml dichloromethane and the mixture was stirred for 3 h at room temperature. The solution was washed with water (20 ml), saturated aqueous sodium hydrogencarbonate solution (20 ml) and brine (20 ml), dried (magnesium sulfate) and evaporated. Chromatography of the residue afforded 1.15 g (62 %) of the title compound as a yellow oil.

MS m/e (%): 720 ($M+H^+$, 100).

d) N-(6-Benzylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

To a solution of 973 mg (1.35 mmol) benzyl-(5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-carbamic acid benzyl ester in 13

ml methanol and 1 ml N,N-dimethylformamide was added 40 mg 10 % palladium on activated charcoal and the mixture was hydrogenated (room temperature, 1 bar) for 1 h. Filtration of the catalyst and evaporation of the filtrate afforded 795 mg (quantitative) of the title compound as a yellow oil.

MS m/e (%): 586 ($M+H^+$, 100).

e) N-(6-Amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

A solution of 750 mg (1.28 mmol) N-(6-benzylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide in 25 ml of a 5 N solution of hydrochloric acid in ethanol was evaporated to dryness and the residue was dissolved in 30 ml methanol and hydrogenated in the presence of 60 mg 10 % palladium on activated charcoal (room temperature, 10 bar) for 20 h. After filtration of the catalyst and evaporation of the solvent the residue was dissolved in 30 ml ethyl acetate, washed twice with saturated aqueous sodium hydrogencarbonate solution and dried (magnesium sulfate). Evaporation of the solution afforded 514 mg (81 %) of the title compound as light brown crystals.

MS m/e (%): 496 ($M+H^+$, 100).

f) N-(6-Acetylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

To a solution of 100 mg (0.20 mmol) N-(6-amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide in 3 ml dichloromethane were added 27 mg (0.21 mmol) N-ethyldiisopropylamine and 70 mg (0.69 mmol) acetic anhydride. After stirring overnight, the solvent was evaporated and the residue was purified by flash-chromatography to give 100 mg (92 %) of the title compound as white solid.

MS m/e (%): 537 (M^+, 68), 282 (100).

Example 11

N-[6-(Acetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide

To a solution of 60 mg (0.11 mmol) N-(6-acetylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide in 2 ml tetrahydrofuran at room temperature under argon were added dropwise 0.13 ml (0.12 mmol) of a 1 M solution of potassium hexamethyldisilazide in tetrahydrofuran. Stirring was continued for 1 h at room

temperature and 17 mg (0.12 mmol) methyl iodide were added. After stirring overnight, the solvent was evaporated and the residue was purified by flash-chromatography to give 40 mg (65 %) of the title compound as white foam.

MS m/e (%): 574 ($M+Na^+$, 17), 552 ($M+H^+$, 100).

Example 12

Cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-amide

To a solution of 100 mg (0.20 mmol) N-(6-amino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide in 3 ml dichloromethane were added 2 ml pyridine and 23 mg (0.22 mmol) cyclopropanecarboxylic acid chloride at 0 °C. After stirring for 2 days at room temperature, the solvent was removed *in vacuo* and the residue was purified by flash-chromatography to give 61 mg (54 %) of the title compound as white solid.

MS m/e (%): 586 ($M+Na^+$, 25), 564 ($M+H^+$, 100).

Example 13

Cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-methyl-amide

The title compound was prepared as a white foam in comparable yield according to the procedure described above for the preparation of N-[6-(acetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide using cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-amide instead of N-(6-acetylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide.

MS m/e (%): 600 ($M+Na^+$, 22), 578 ($M+H^+$, 100).

Example 14

2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-imidazol-1-yl-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide

a) 6-Imidazol-1-yl-4-o-tolyl-pyridin-3-ylamine

The title compound was obtained as light brown foam according to the procedures described above for the preparation of 6-morpholin-4-yl-4-o-tolyl-pyridin-3-ylamine (Example 7, step e)) using imidazole instead of morpholine in step a).

MS m/e (%): 251 ($M+H^+$, 100).

b) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-imidazol-1-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide

The title compound was obtained as yellow crystals according to the procedure described above for the preparation of 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide (Example 7, step g)) using 6-imidazol-1-yl-4-o-tolyl-pyridin-3-ylamine instead of methyl-(6-morpholin-4-yl-4-o-tolyl-pyridin-3-yl)-amine.

MS m/e (%): 532 (M^+, 100).

c) 2-(3,5-Bis-trifluoromethyl-phenyl)-N-(6-imidazol-1-yl-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide

The title compound was obtained as white crystals according to the procedure described above for the preparation of N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-N-methyl-4-o-tolyl-nicotinamide (Example 1, step c)) using 2-(3,5-bis-trifluoromethyl-phenyl)-N-(6-imidazol-1-yl-4-o-tolyl-pyridin-3-yl)-isobutyramide instead of 6-chloro-N-methyl-4-o-tolyl-nicotinamide and methyl iodide instead of 3,5-bis(trifluoromethyl)benzyl bromide.

MS m/e (%): 547 ($M+H^+$, 100).

Example A

Tablets of the following composition are manufactured in the usual manner:

	mg/tablet
Active substance	5
Lactose	45
Corn starch	15
Microcrystalline cellulose	34
Magnesium stearate	1
Tablet weight	100

Example B

Capsules of the following composition are manufactured:

	mg/capsule
Active substance	10
Lactose	155
Corn starch	30
Talc	5
Capsule fill weight	200

The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

Example C

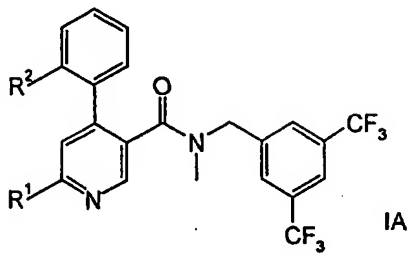
Suppositories of the following composition are manufactured:

		mg/supp.
Active substance		15
Suppository mass		1285
	Total	1300

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

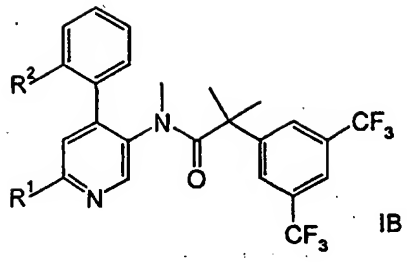
Claims

1. Compounds of the general formulas



IA

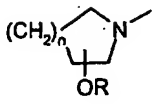
or



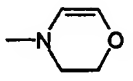
IB

wherein

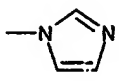
R^1 is



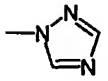
,



,



,



or is

$-NH(CH_2)_2OH$, $-NR^3C(O)CH_3$ or $-NR^3C(O)$-cyclopropyl;

R^2 is methyl or chloro;

R^3 is hydrogen or methyl;

R is hydrogen or $-(CH_2)_2OH$; and

n is 1 or 2

and pharmaceutically acceptable acid addition salts thereof.

2. A compound of formula IA according to claim 1, wherein R^2 is methyl.

3. A compound according to claim 2, which is

N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-4-o-tolyl-6-[1,2,4]triazol-1-yl-nicotinamide,
N-(3,5-bis-trifluoromethyl-benzyl)-6-(2-hydroxy-ethylamino)-N-methyl-4-o-tolyl-nicotinamide,

4-hydroxy-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide,
4-(2-hydroxy-ethoxy)-4'-o-tolyl-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide or
(R)-N-(3,5-bis-trifluoromethyl-benzyl)-6-(3-hydroxy-pyrrolidin-1-yl)-N-methyl-4-o-tolyl-nicotinamide.

4. A compound of formula IA according to claim 1, wherein R^2 is chloro.

5. A compound according to claim 4, which is

4'-(2-chloro-phenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

6. A compound of formula IB according to claim 1, wherein R^2 is methyl.

7. A compound according to claim 6, which is

2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-ethylamino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2,3-dihydro-[1,4]oxazin-4-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide,
N-(6-acetylamino-4-o-tolyl-pyridin-3-yl)-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide,
N-[6-(acetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-isobutyramide,
cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-amide,
cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-methyl-amide or
2-(3,5-bis-trifluoromethyl-phenyl)-N-(6-imidazol-1-yl-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide.

8. A compound of formula IB according to claim 1, wherein R^2 is chloro.

9. A compound according to claim 8, which is

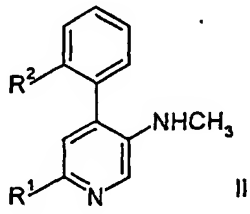
2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(2-hydroxy-ethylamino)-pyridin-3-yl]-N-methyl-isobutyramide.

10. A medicament containing one or more compounds as claimed in any one of claims 1-9 and pharmaceutically acceptable excipients.

11. A medicament according to claim 10 for the treatment of diseases related to NK-1 receptor antagonists.

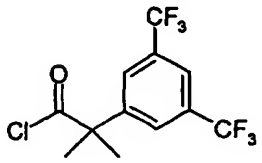
12. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



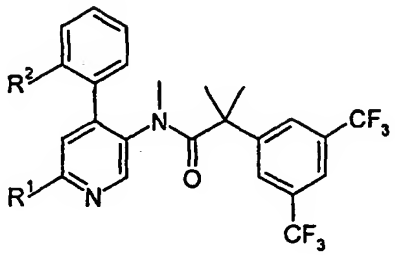
II

with a compound of formula



III

to a compound of formula

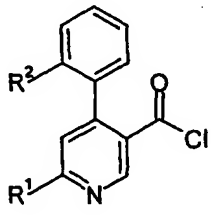


IB

wherein R^1 and R^2 have the significances given in claim 1,

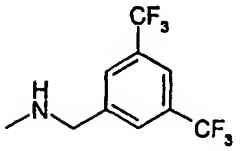
or

b) reacting a compound of formula



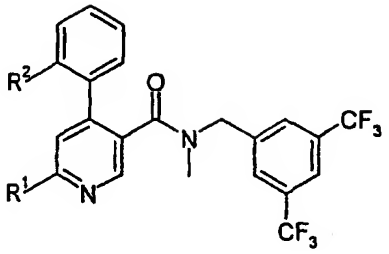
IV

with a compound of formula



V

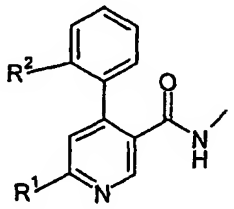
to give a compound of formula



IA

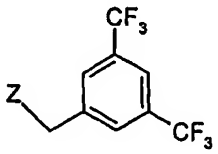
wherein R^1 and R^2 have the significances given in claim 1, or

c) reacting a compound of formula



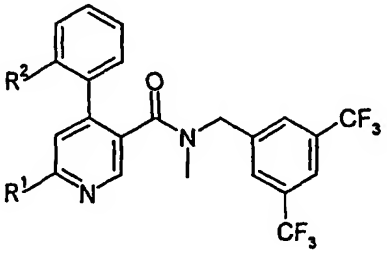
VI

with a compound of formula



VII

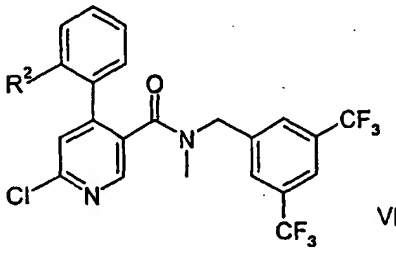
to a compound of formula



IA

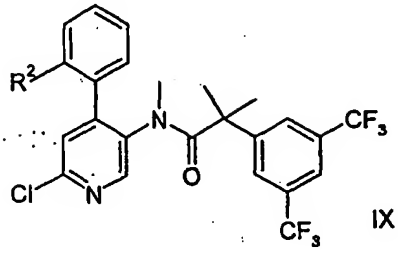
wherein Z is Cl, Br, I, $-OS(O)_2C_6H_4CH_3$ or $-OS(O)_2CH_3$ and the other definitions of substituents are given in claim 1, or

d) reacting a compound of formula



VIII

or

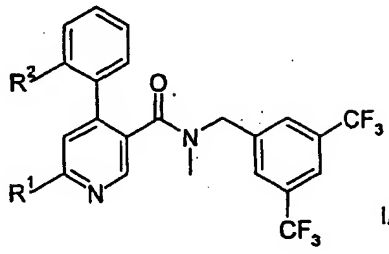


IX

with a compound of formula

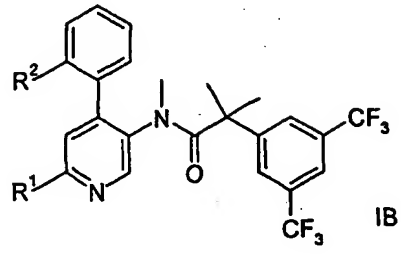
R^1H XIV

to a compound of formulas



IA

or



IB

wherein the definition of substituents is given in claim 1,

and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

13. A compound according to any one of claims 1-9, whenever prepared by a process as claimed in claim 12 or by an equivalent method.

14. The use of a compound in any one of claims 1-9 for the treatment of diseases related to NK-1 receptor antagonists.

15. The use of a compound in any one of claims 1-9 for the manufacture of medicaments containing one or more compounds of formula I for the treatment of diseases related to NK-1 receptor antagonists.

16. The invention as hereinbefore described.

5 ***

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/EP 01/08432

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D521/00 C07D213/82 C07D401/04 C07D213/75 C07D413/04
A61K31/4427 A61K31/465 A61P25/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DE 100 08 042 A (HOFFMANN LA ROCHE) 31 August 2000 (2000-08-31) examples 28,32,34,45,47 claims 1-11	1-3,6, 10-12
A	IKEURA Y ET AL: "POTENT NK1 RECEPTOR ANTAGONISTS: SYNTHESIS AND ANTAGONISTIC ACTIVITY OF VARIOUS HETEROCYCLES WITH AN N-3,5-BIS(TRIFLUOROMETHYL)BENZYL-N-METHYLCARBAMOYL SUBSTITUENT" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 45, no. 10, 1997, pages 1642-1652, XP000910111 ISSN: 0009-2363 abstract; example 1C	1,11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 November 2001	03/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	NATSUGARI H ET AL: "NOVEL, POTENT, AND ORALLY ACTIVE SUBSTANCE P ANTAGONISTS: SYNTHESISAND ANTAGONIST ACTIVITY OF N-BENZYLCARBOXAMIDE DERIVATIVES OF PYRIDO3,4-BPYRIDINE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, no. 16, 1995, pages 3106-3120, XP000910106 ISSN: 0022-2623 abstract; example 1J	1,11
A	HOSOKI R ET AL: "PHARMACOLOGICAL PROFILES OF NEW ORALLY ACTIVE NONPEPTIDE TACHYKININNK1 RECEPTOR ANTAGONISTS" EUROPEAN JOURNAL OF PHARMACOLOGY, AMSTERDAM, NL, vol. 341, no. 2/3, 1998, pages 235-241, XP000909816 ISSN: 0014-2999 abstract; example II	1,11
A	WO 99 47132 A (NATSUGARI HIDEAKI ;DOI TAKAYUKI (JP); IKEURA YOSHINORI (JP); TAKED) 23 September 1999 (1999-09-23) reference example 12 claims 23-32	1,11

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/EP 01/08432

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 10008042 A	31-08-2000	AU 1946800 A	31-08-2000
		BG 104187 A	30-11-2000
		BR 0000908 A	12-09-2000
		CN 1270959 A	25-10-2000
		DE 10008042 A1	31-08-2000
		EP 1035115 A1	13-09-2000
		FR 2790473 A1	08-09-2000
		GB 2347422 A	06-09-2000
		HR 20000097 A1	31-10-2001
		HU 0000748 A2	28-03-2001
		JP 2000247957 A	12-09-2000
		NO 20000885 A	25-08-2000
		PL 338598 A1	28-08-2000
		SK 2352000 A3	12-09-2000
		US 6297375 B1	02-10-2001
		US 6310664 B1	30-10-2001
WO 9947132 A	23-09-1999	AU 2853299 A	11-10-1999
		BR 9908895 A	05-12-2000
		CN 1291099 T	11-04-2001
		EP 1061926 A2	27-12-2000
		HU 0100934 A2	28-09-2001
		JP 11322748 A	24-11-1999
		WO 9947132 A2	23-09-1999
		NO 20004144 A	10-10-2000